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Author	佐藤, 良博(Sato, Yoshihiro) 園田, よし子(Sonoda, Yoshiko)
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Synthesis of Lanosterol Analogs with Lengthened Side Chains and their Effects on Cholesterol Biosynthesis from Lanosterol*

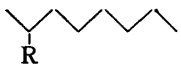
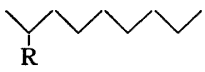
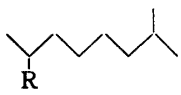
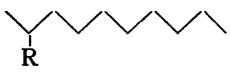
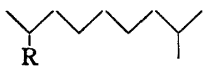
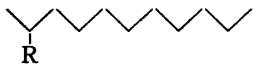
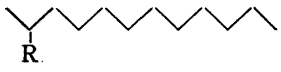
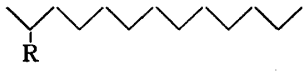
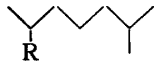
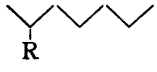
Yoshihiro SATO and Yoshiko SONODA

佐藤良博，園田よし子

The biosynthesis of cholesterol from lanosterol involves the removal of three methyl groups, reduction of the Δ^{24}-double bond, and the migration of double bonds. However, very few studies have been carried out on the inhibition of cholesterol biosynthesis from lanosterol.

Recently, we reported the effects of lanosterol analogs, cholesterol analogs, and

Table I Cholesterol Biosynthesis during Incubation of S_{10} Fraction of Rat Liver Homogenate with [24-^{3}H]-Lanosterol in the Presence of Various Lanosterol Analogs

Compound		Lanosterol Fr.(%)	Cholesterol Fr.(%)	Inhibition (%)
None (control)		24.9	22.1	—
	**10**(C_{30})	29.8	17.9	19
	**11**(C_{31})	28.5	20.2	9
	**12**(C_{31})	32.4	16.0	28
	**13**(C_{32})	26.9	20.4	8
	**14**(C_{32})	33.6	20.3	8
	**15**(C_{33})	27.3	19.6	12
	**16**(C_{34})	27.8	22.3	0
	**17**(C_{35})	21·6	24.7	0
	**18**(C_{30})	32.6	18.3	17
	**19**(C_{29})	75.2	5.1	77

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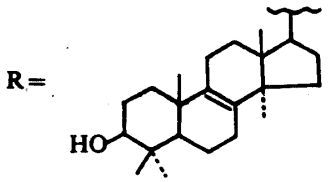

oxygenated lanosterol derivatives on cholesterol biosynthesis from lanosterol. From these studies, it was clear that both the side chain and skeleton structures are important in relation to the inhibitory effect. This study was carried out in order to determine whether lanosterol analogs with longer side chains than that of lanosterol could have an inhibitory effect.

The effects of the lanosterol analogs on cholesterol biosynthesis from lanosterol were examined and the results are shown in Table I. Further, 24,25-dihydrolanosterol (**18**) and 27-nor-24,25-dihydrolanosterol (**19**) were tested as references. The present results coupled with our previous ones may be summarized as follows. Among the lanosterol analogs, the 24-ethylidene-, nor-, dinor-, tetranor-, and pentanor-compounds showed inhibitory effects. In particular, 27-nor-24,25-dihydrolanosterol (**19**) showed the most potent inhibitory effect in the series of analogs. These results are summarized in Fig. 1. Further, cholesterol analogs with various sizes of side chain showed no inhibitory activity. On the other hand, in a series of oxygenated lanosterol derivatives, 7-oxo-24,25-dihydrolanosterol was the most active inhibitor (98% inhibition of cholesterol synthesis from lanosterol).

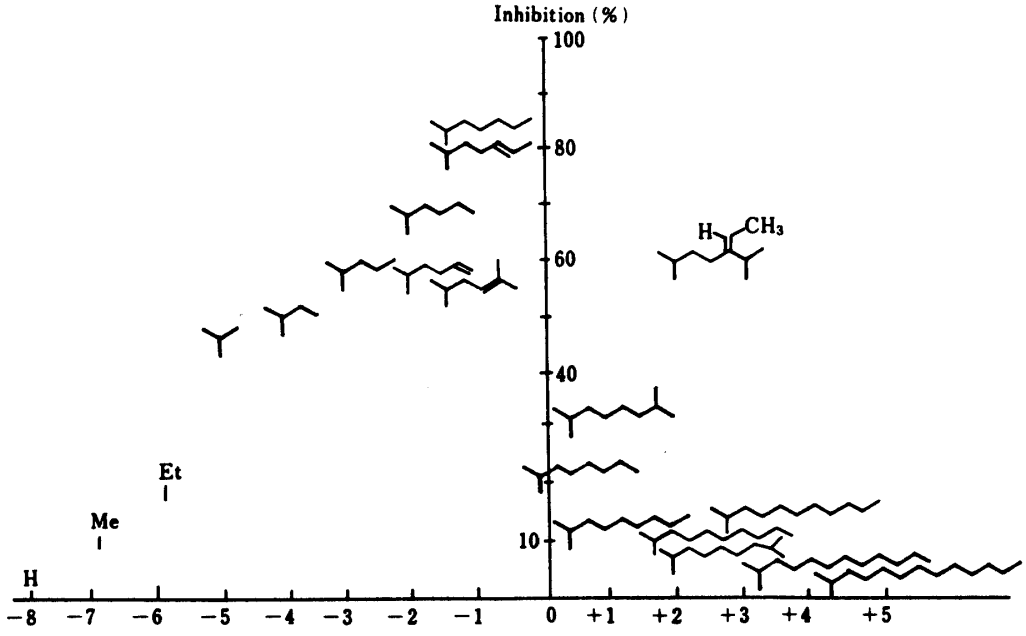

Fig. 1. Relationship between Side Chain Structure and Inhibition of Cholesterol Biosynthesis

In the experiments in the presence of active inhibitors, recovery yields of the substrate ([24-^{3}H]-lanosterol) increased in parallel to the extents of inhibitions. The results suggest that a potent inhibitor such as the 7-oxo-compound or 27-nor-compound may inhibit 14-demethylation of lanosterol, which is the first step of transformation of lanosterol to cholesterol, although the S-10 fraction used in this study contains many enzymes. From our studies together with other results, the enzyme involved in the initial step of the 14-demethylation is thought to be a cytochrome P-450. The substrate binding site contains at least two pockets involved in the binding of the lanosterol skeleton and its side chain. The pocket for the side chain is thought to reach the region of C-22 from the terminal area of the side chain. In the case of the hexanor-, heptanol-, and octanor-compounds, thus, no inhibitory effect is observed since their side chains are too short to interact with the binding site at the pocket. Further, no inhibitory effect is observed with the analogs having longer side chains than lanosterol, since their side chains are too long to be satisfactorily accommodated in the binding site. On the other hand, 20-iso-24,25-dihydrolanosterol, having a different orientation at the 20-position from 24,25-dihydrolanosterol, showed no inhibitory effect. Among the oxygenated lanosterol derivatives studied, 7-oxo-24,25-dihydrolanosterol showed the highest inhibitory activity, and it is suggested that this effect is due to its interaction with an active center of cytochrome P-450, based on previously reported results.

In summary, it is suggested that the important features for an inhibitory effect of lanosterol and cholesterol derivatives on the cholesterol biosynthesis from lanosterol are the side chain and skeletal structures, and the configuration at C-20.